Integrating Genomics into the Pediatric Oncology Clinic

Jack Shern MD

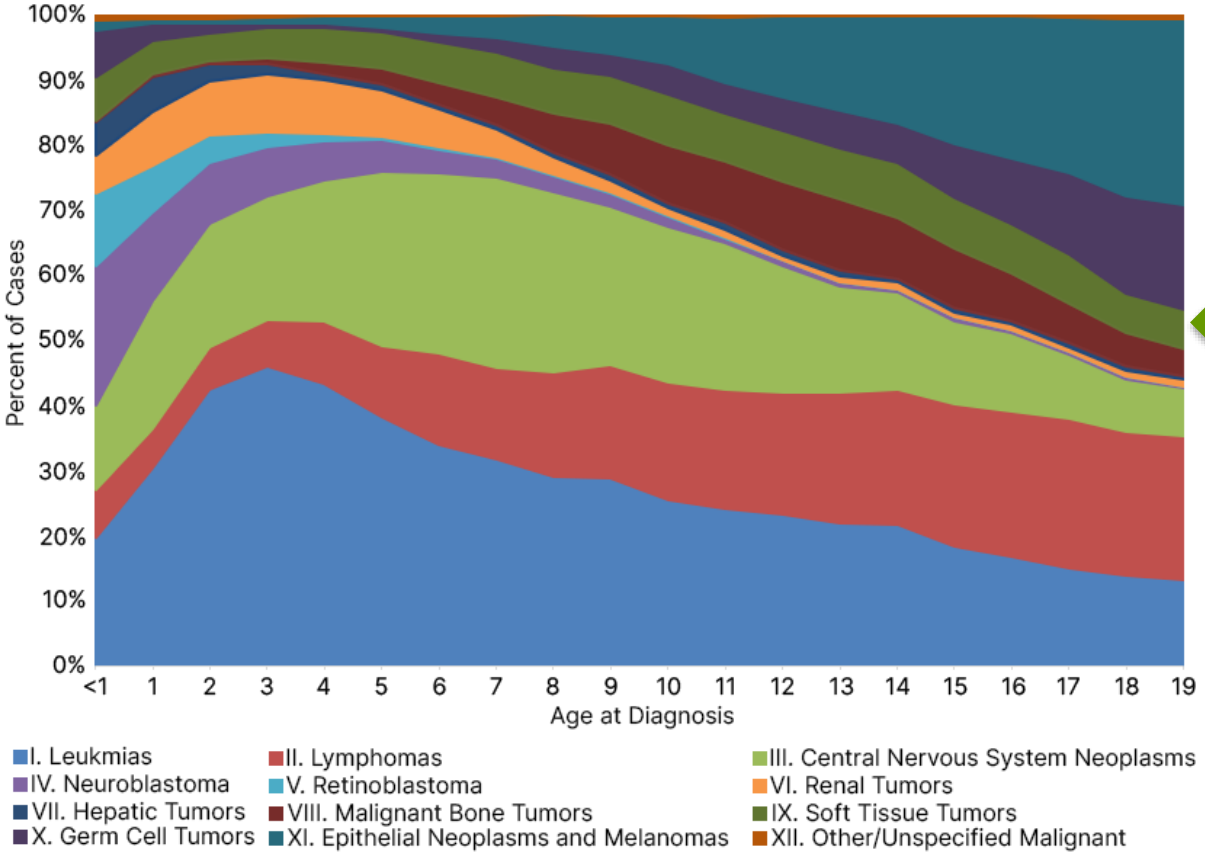
Lasker Clinical Research Scholar

Pediatric Oncology Branch

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

September 1, 2021

Soft tissue sarcomas represent ~7% of all pediatric cancer cases



Soft tissue sarcomas

https://seer.cancer.gov/statistics/nccr/

Two strategies for making progress for patients with rare pediatric tumors

1. Develop disease specific therapies; new therapeutic strategies
2. Improve the accuracy of diagnosis; disease classification/staging; and disease detection
   - Genomic risk stratification of rhabdomyosarcoma
   - Use of cell free DNA in early cancer detection for patients with Neurofibromatosis Type 1 (NF1)

Rhabdomyosarcoma the most common soft tissue sarcoma of childhood

Finn Schafran

Week

1	2	3	4	5	6	7	8	9	10	11	12	13	15
V	V	V	V	V	V	V	V	V	V	V	V	V	
A			A									A	Evaluation
C			C			C			C			C	
			Radiation Therapy →										

Week

16	17	18	19	20	21	22	23	24	25	26	27	28	30
V			V	V	V	V	V	V	V			V	
A			A			A			A			A	Evaluation
C			C			C			C			C	

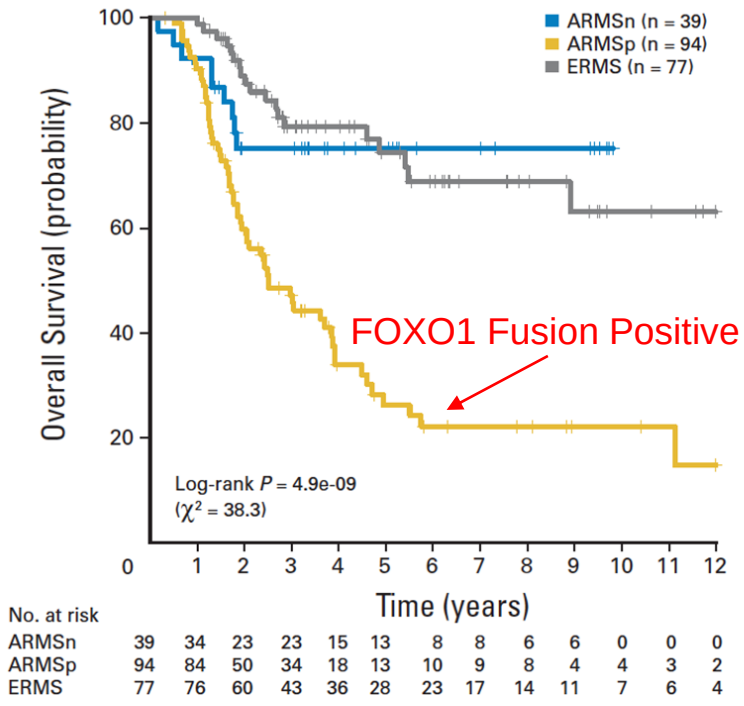
Week

31	32	33	34	35	36	37	38	39	40	41	42	43
V	V	V	V	V	V	V			V			
A			A			A			A			End of Therapy Evaluation
C			C			C			C			

	Drug	Age	Dose
V	VinCRIStine	< 1 year ≥ 1 year and < 3 years ≥ 3 years	0.025 mg/kg IV x 1 0.05 mg/kg IV x 1 (maximum dose 2 mg) 1.5 mg/m^2 IV x 1 (maximum dose 2 mg)
A	Dactinomycin	< 1 year ≥ 1 year	0.025 mg/kg IV x 1 0.045 mg/kg (maximum dose 2.5 mg) IV X 1
C	Cyclophosphamide	< 3 years ≥ 3 years	40 mg/kg IV X 1 1200 mg/m^2 IV X 1
Mesna and fluids will be used with Cyclophosphamide			
Neutrophil growth factor will be used in VAC and VC cycles. See Section 8 for specific directions.			
If there is an age change during treatment, use the new appropriate age dosing in the next cycle			

Current rhabdomyosarcoma risk stratification is imprecise

Risk Group	FOXO1 Fusion Status	Stage	Group	Proportion of patients	EFS
Low Risk	Fusion Negative	1	I, II, III (orbit only)	32%	70-95%
	Fusion Negative	2	I, II		
Intermediate Risk	Fusion Negative	1	III (non-orbit)	27%	73%
		2,3	III		
		3	I, II		
		4	IV (age <10 years)		
	Fusion Positive	1,2,3	I, II, III	25%	65%
High Risk	Fusion Positive	4	IV	8%	15%
	Fusion Negative	4	IV (age ≥10 years)	8%	35%



Williamson D et al. JCO 2010

An International collaboration to profile rhabdomyosarcoma

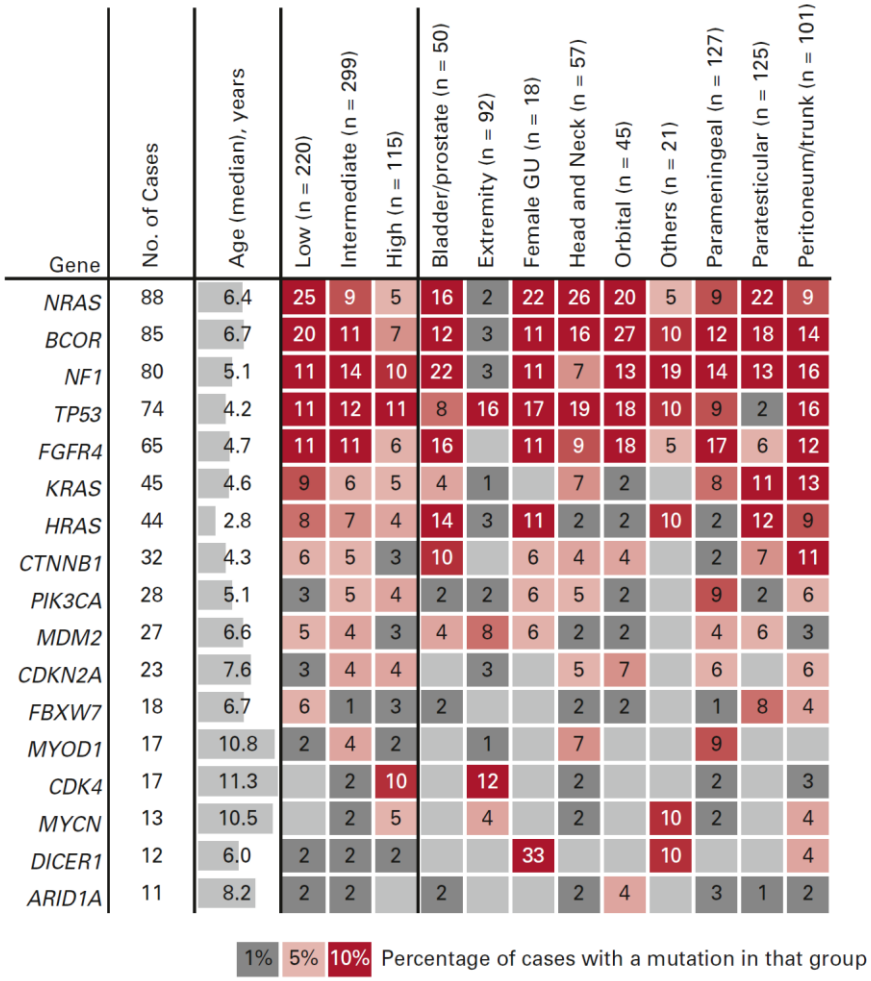
CHILDREN'S ONCOLOGY GROUP

ICR The Institute of Cancer Research

NIH NATIONAL CANCER INSTITUTE Center for Cancer Research

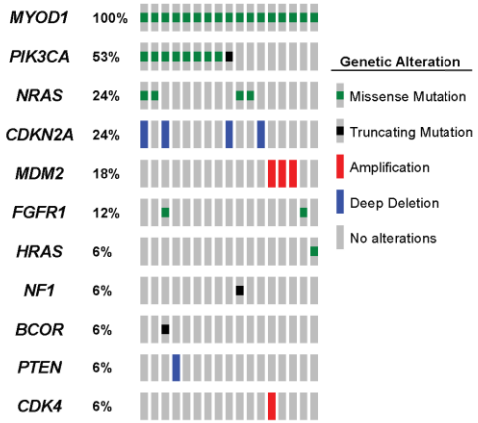
TABLE 1. Clinical Characteristics of Included Patients

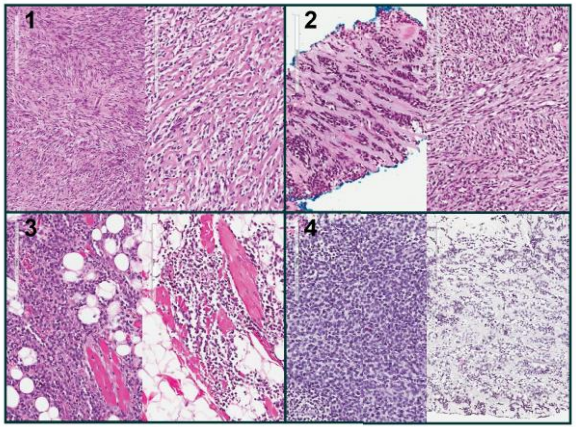
Characteristic	All (N = 641)	COG (n = 344)	UK (n = 297)
Sex, No. (%)			
Male	421 (66)	232 (66)	189 (66)
Female	220 (34)	112 (34)	108 (34)
Age at presentation, years			
Median	5.9	6.4	5.3
Range	0.02-37.8	0.02-37.8	0.1-23.1
Tumor histology, No. (%)			
Alveolar	151 (24)	68 (20)	83 (28)
Embryonal	447 (70)	254 (74)	187 (63)
Mixed alveolar and embryonal	3 (< 1)	2 (1)	1 (< 1)
Spindle cell RMS	18 (3)	18 (5)	7 (2)
NOS	20 (3)	2 (1)	18 (6)
Pleomorphic	2 (< 1)	0 (< 1)	1 (< 1)

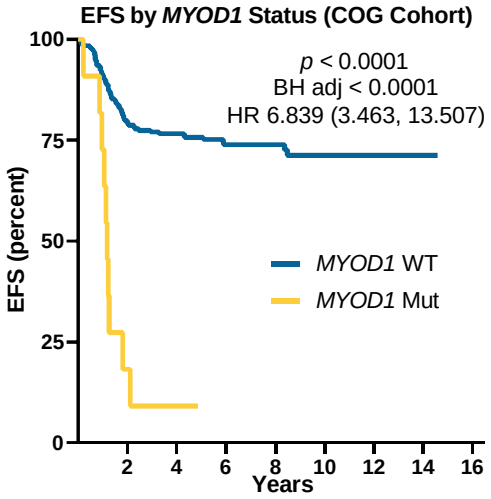


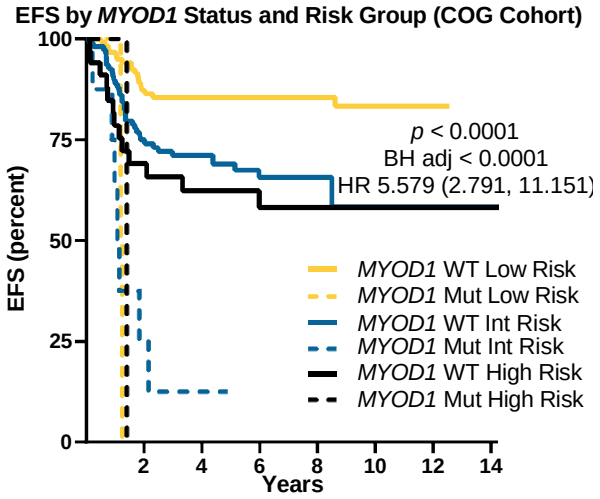
MYOD1 L122R mutant rhabdomyosarcoma

- 3% of all fusion negative cases
- Older age of presentation
- Histopathology is not specific
- Cases can present as low, intermediate or high risk





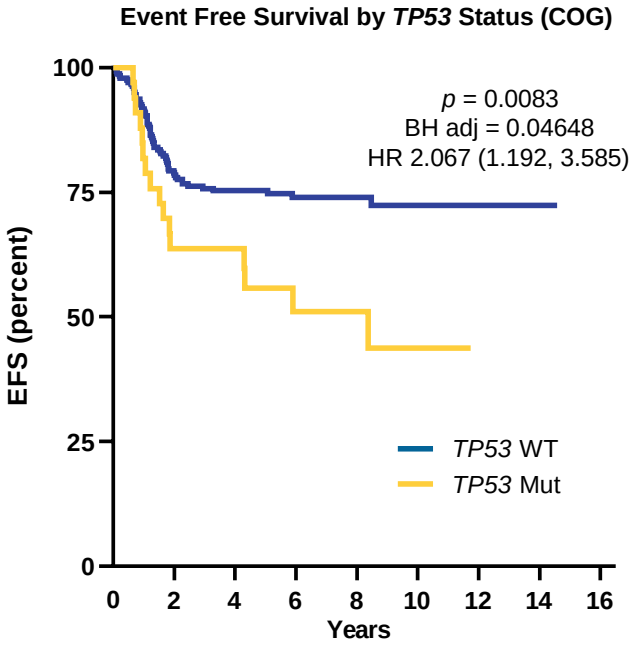


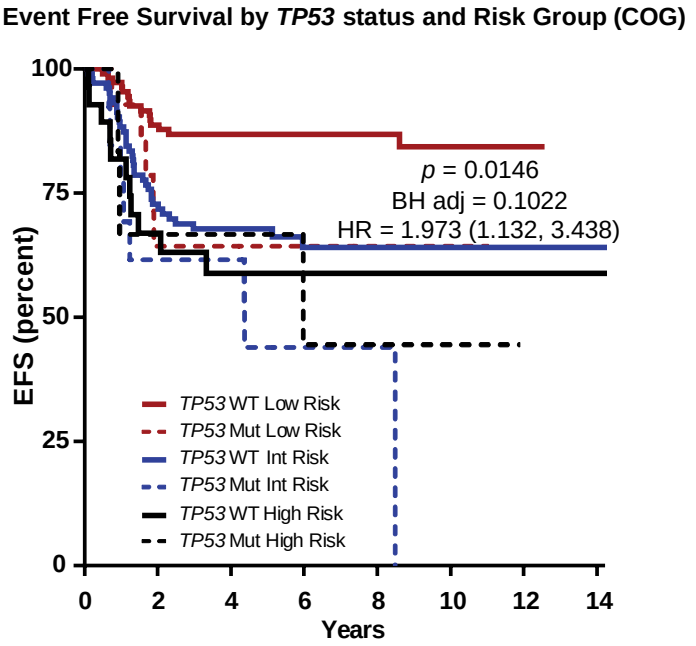


Shern et al., JCO 2021

TP53 mutations are a genomic marker of more aggressive disease in fusion negative rhabdomyosarcoma

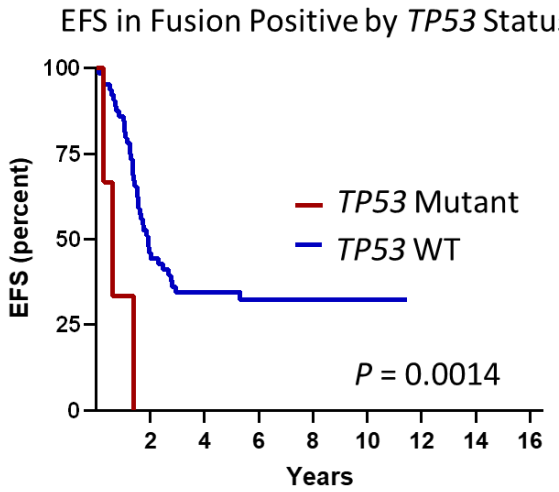
- *TP53* mutations occur in 13% of all fusion negative cases
- Mutations are frequently found in tumors with a second oncogenic mutation
- ~40% of fusion negative cases that occur on the extremity are *TP53* mutant or *MDM2* amplified

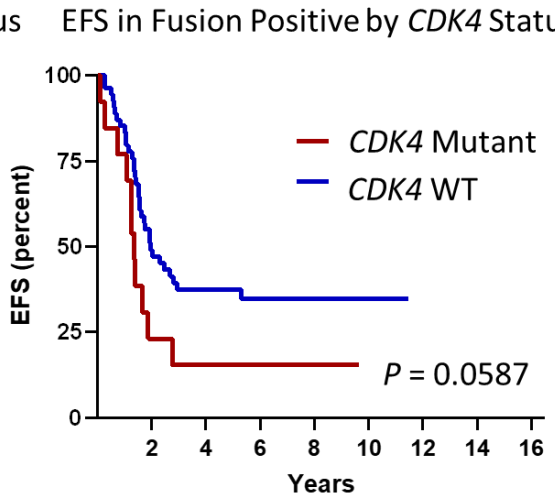


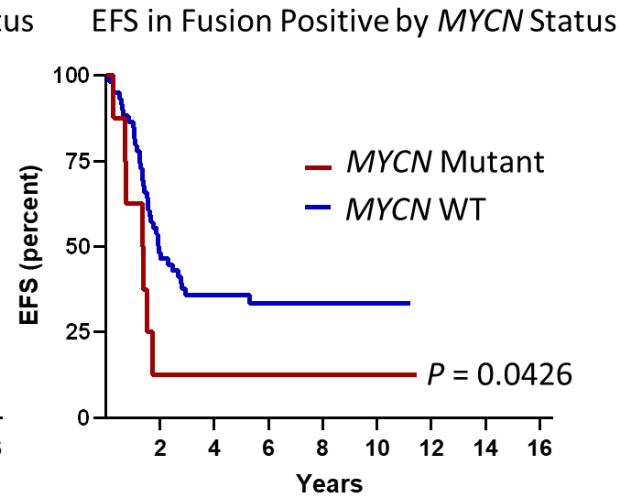


Shern et al., JCO 2021

TP53 mutation or focal amplification of *CDK4* or *MYCN* are genomic markers of worse outcome in fusion positive cases







Shern et al., JCO 2021

Refining rhabdomyosarcoma risk stratification

TABLE A4. Proposed Risk Stratification With the Incorporation of Genetic Markers

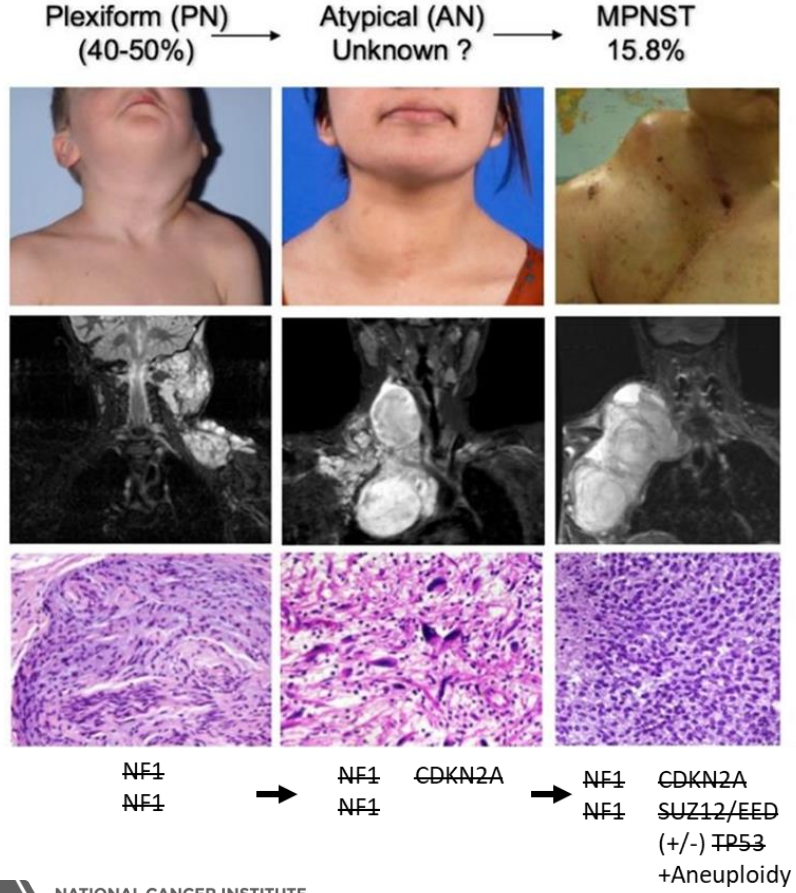
Risk Stratification	FFS, %	Fusion Status	Stage	Group	Anatomy	Metastatic Sites	Genetic Marker
Low	> 85						
		Negative	I or II	I or II			
		Negative	I	III	Orbit only		
Intermediate	60-75						
		Negative	Any	III	Nonorbit		
		Negative	III	I or II			
		Negative	IV	IV		1	
		Negative	Any low risk				*TP53* mutant
		Positive	I, II, or III	I, II, or III			*TP53* WT
High	< 40						
		Negative	IV	IV		> 1	
		Negative	Any intermediate risk				*TP53* mutant
		Positive	IV	IV			*TP53* WT
Ultrahigh	< 20						
		Negative	Any	Any		Any	*MYOD1* mutant
		Positive	Any	Any		Any	*TP53* mutant

Shern et al., JCO 2021

Molecular profiling of Rhabdomyosarcoma: from crawling to running

- New opportunities to study these results in a prospective national trials
  1. New High-Risk Trial (ARST2031) – Wendy Allen-Rhoades, MD (Mayo)
     - Prospectively testing the prognostic value of *TP53*, *MYOD1*, *CDK4* and *MYCN*
  2. New Low-Risk Trial (ARST2032) – Josephine HaDuong, MD (Children's Orange County)
     - Potential for upstaging of *MYOD1* and *TP53* mutations
  3. Actively performing comprehensive genomic characterization of the current Intermediate Risk Study COG ARST1431 – Brian Crompton, MD (Dana Farber)
- Childhood Cancer Data Initiative – Molecular Characterization Protocol
  1. Germline/tumor exome, Methylation Array, and RNA based Fusion panel
     - CLIA results returned with 2 weeks to the treating team
  2. Detailed correlative clinical data will be collected on COG Project:EveryChild

Malignant Peripheral Nerve Sheath Tumors (MPNST)



- ~50% of cases occur in patients with Neurofibromatosis Type 1 (NF1)
- NF1 patients have an 8-13% lifetime risk of developing MPNST
- Chemotherapy and radiotherapy resistant

CNV

Type of Tumor (Number evaluated)	Median number of CNVs per tumor (Range)
PN (22)	9 (3 - 104)
AN (10)	23 (5 - 49)
MPNST (4)	438 (294 - 866)

Pemov et al., 2019

Early detection of Malignant Peripheral Nerve Sheath Tumor

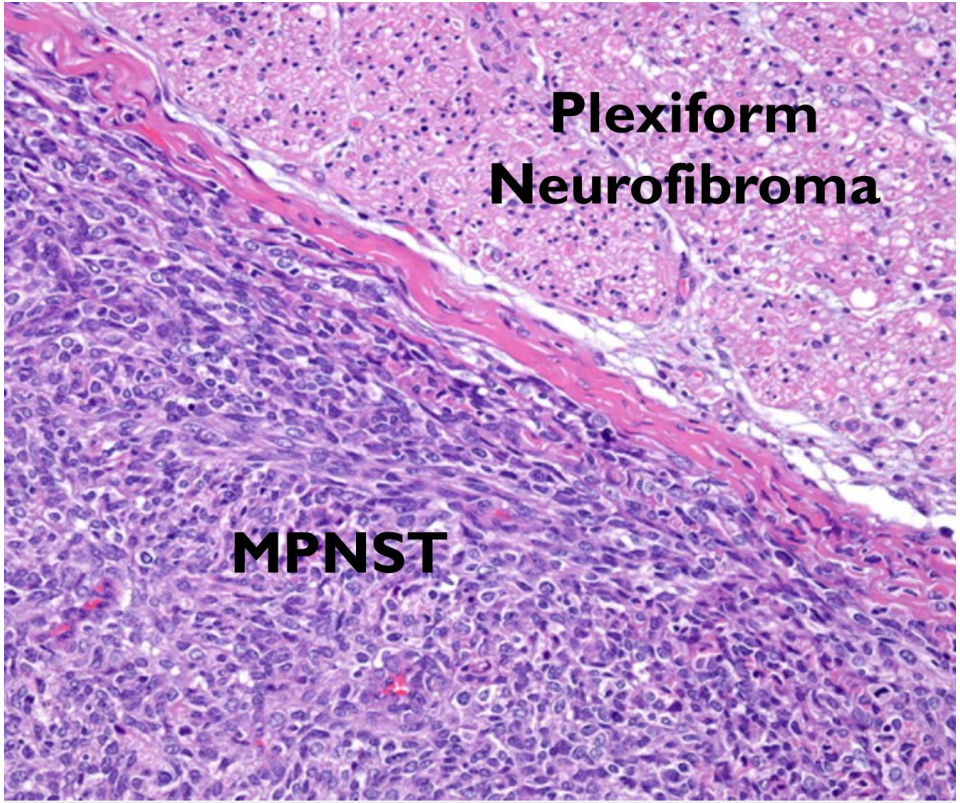
Imaging:

- Patients present with multiple PN, Whole Body-MRI is research only
- PET without standardized guidelines
- Anatomic MRI 90% sensitive, 61% specific[1]

Tissue Biopsies:

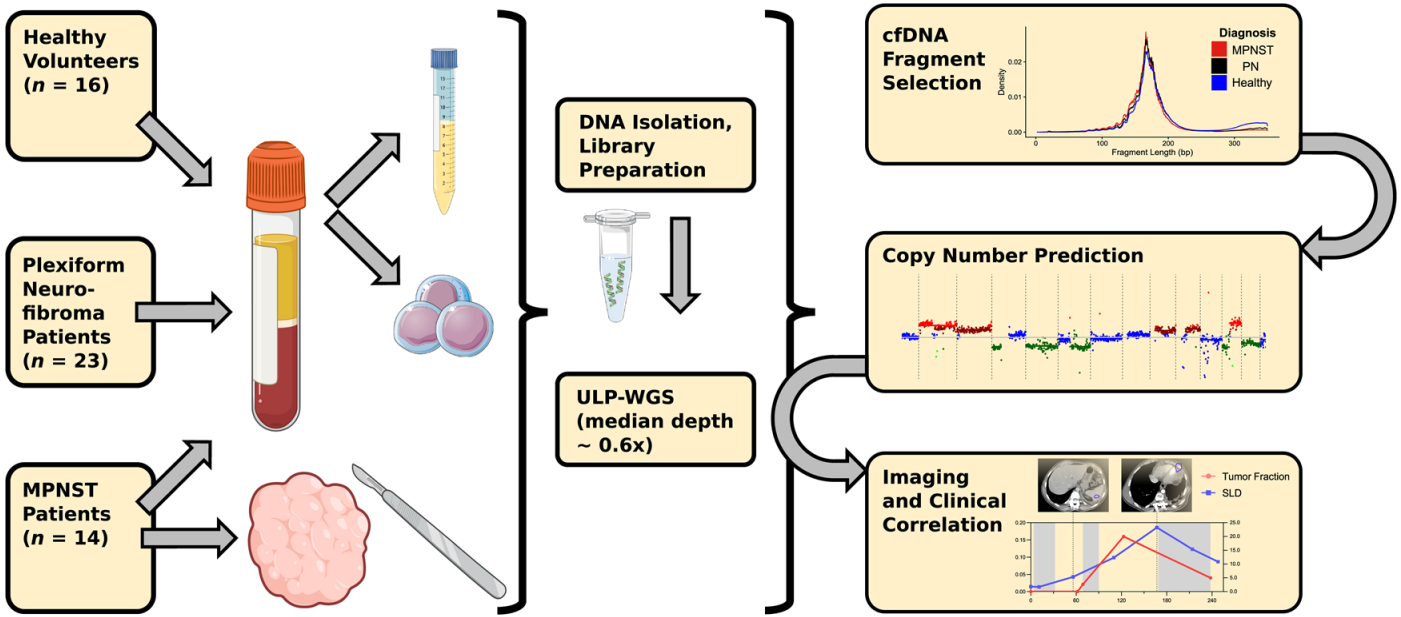
- Invasive with potential morbidity
- High Positive Predictive Value, low Negative Predictive Value due to tumor size and intratumoral heterogeneity

Hypothesis: Changes in <u>plasma cell-free DNA</u> can accurately distinguish Plexiform from MPNST.



[1]Wasa et al., 2010

Cell free DNA to detect NF1 nerve tumors: Study Design

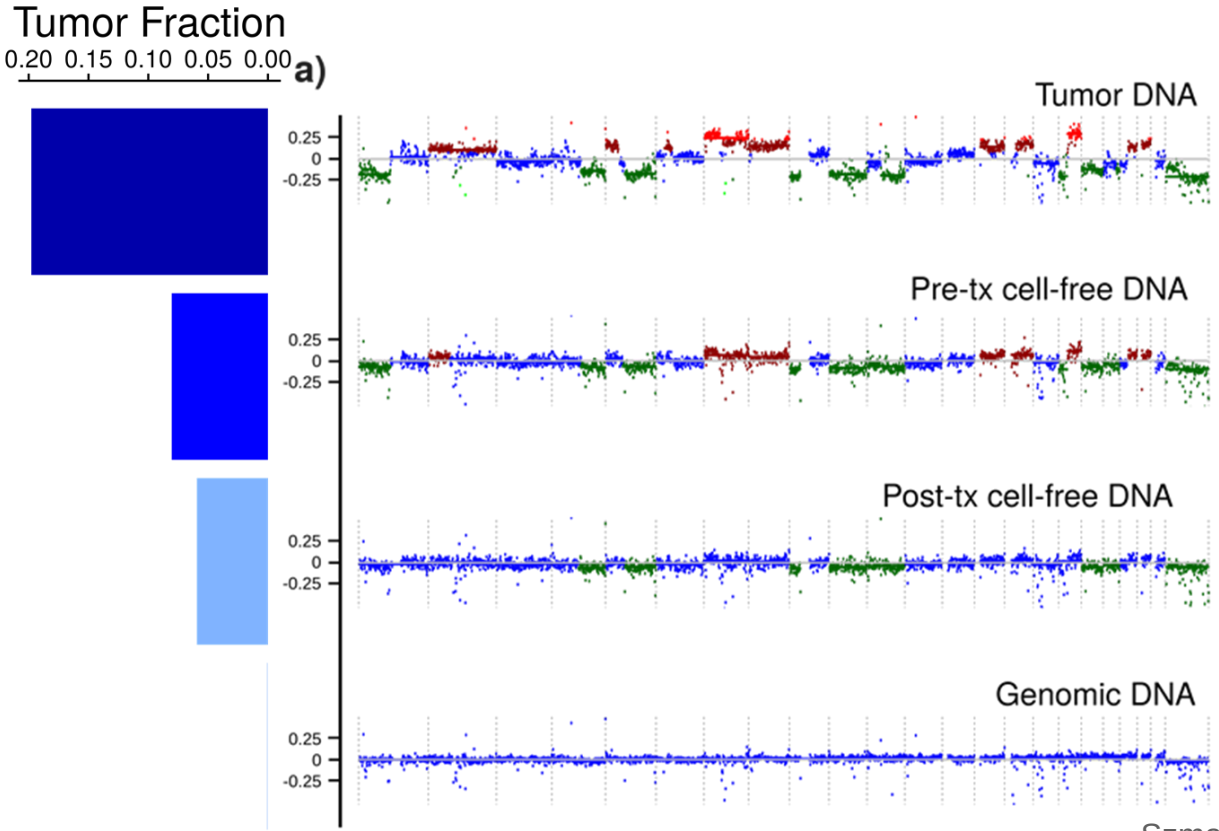


Szmanski et al., PlosMed 2021

Angie Hirbe, MD PhD

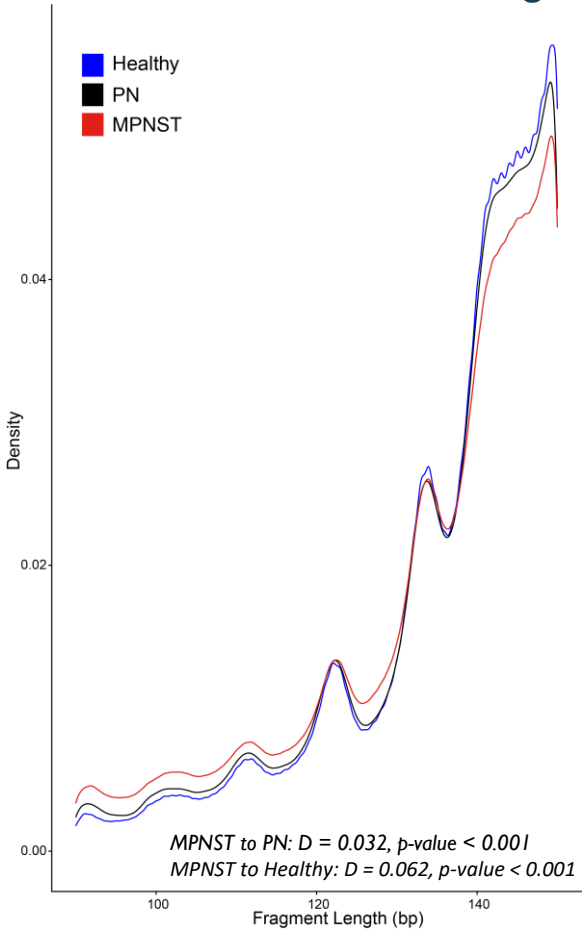
Aadel Chaudhuri, MD PhD

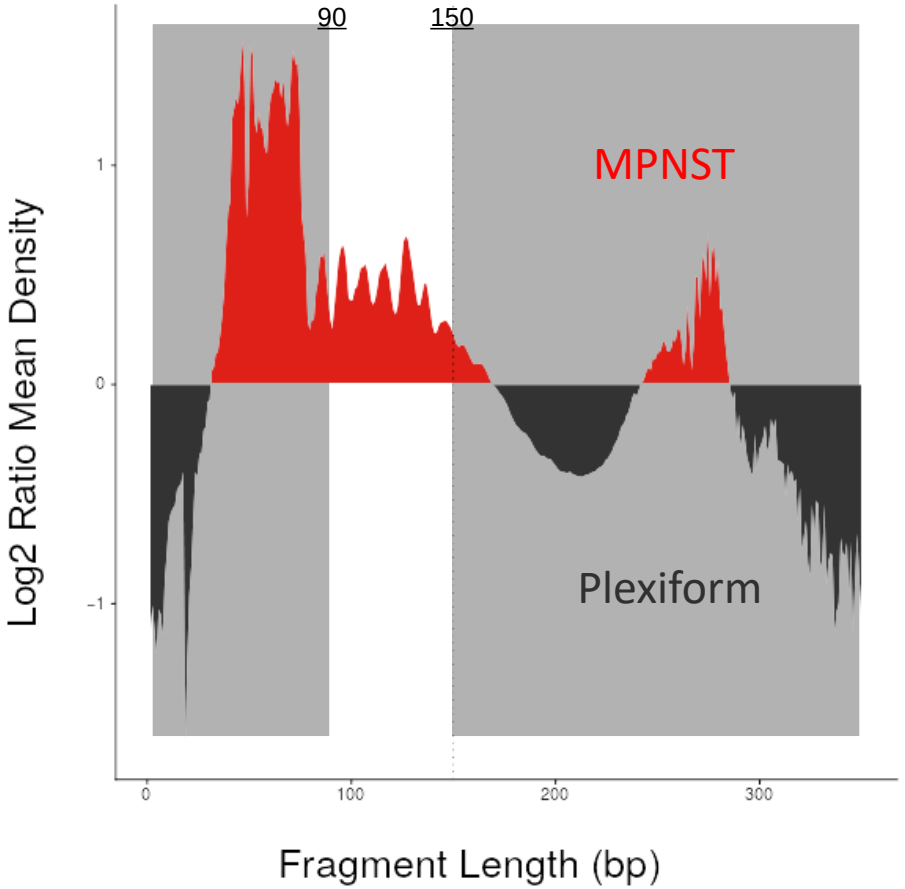
Copy Number Alterations and the Calculated Tumor Fraction correlate well with tumor sequencing



Szmanski et al., PlosMed 2021

Shorter cell free DNA fragments were enriched for in MPNST samples



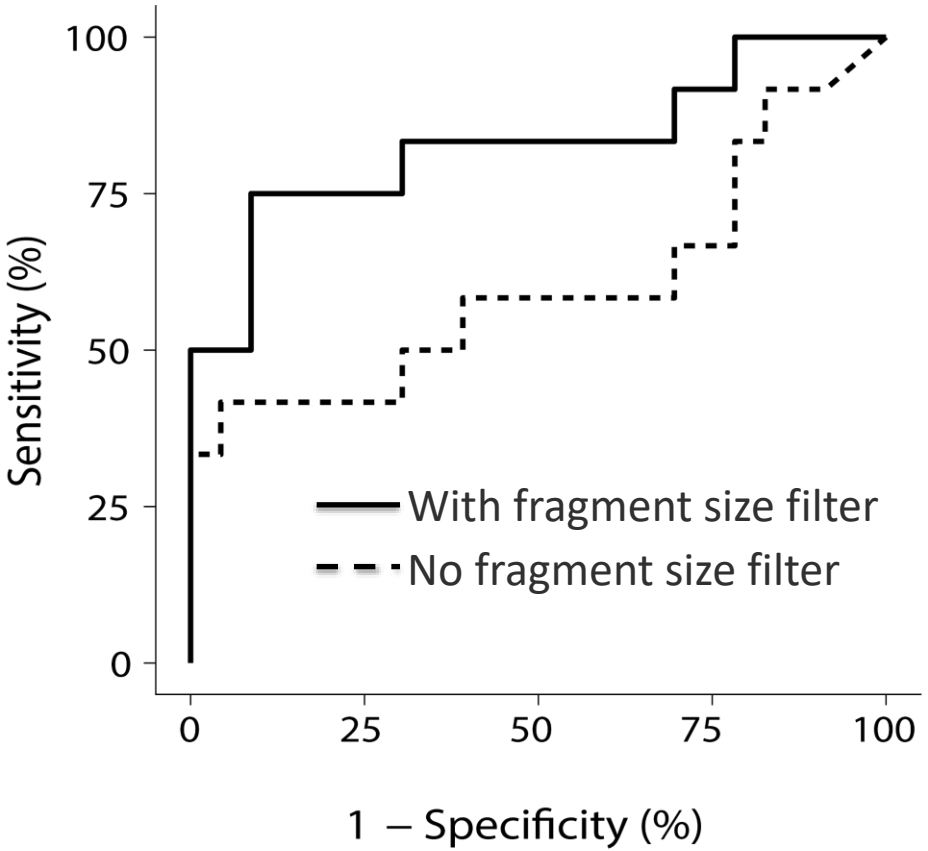


Tumor Fraction Distinguishes Plexiform Neurofibroma from Pre-Treatment MPNST Samples

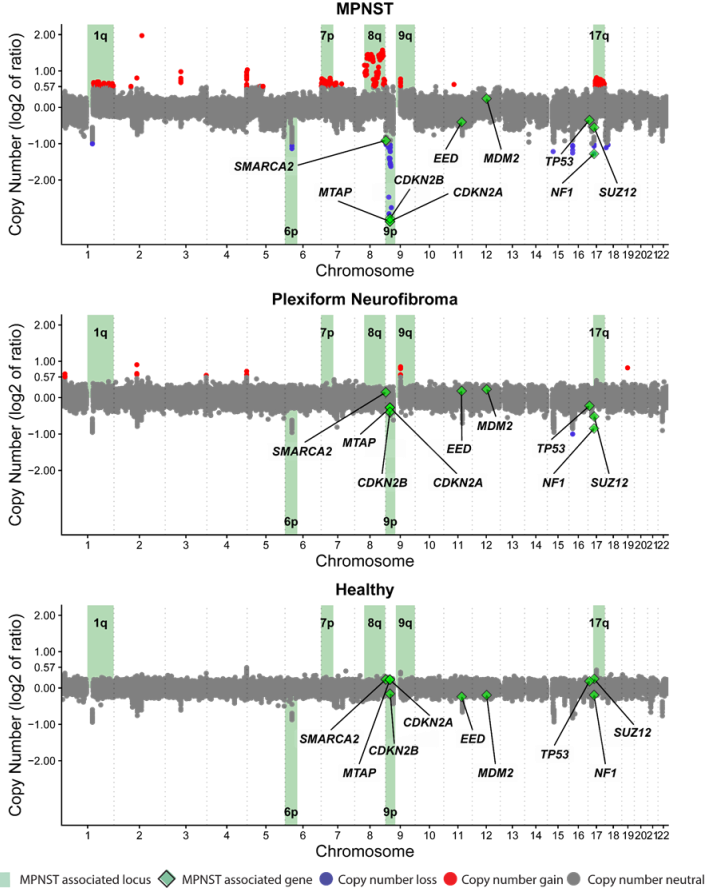
Condition	AUC	Sensitivity	Specificity	Accuracy
Pre-treatment	0.83	75%	91%	86%
Serial analysis	0.89	83%	91%	89%

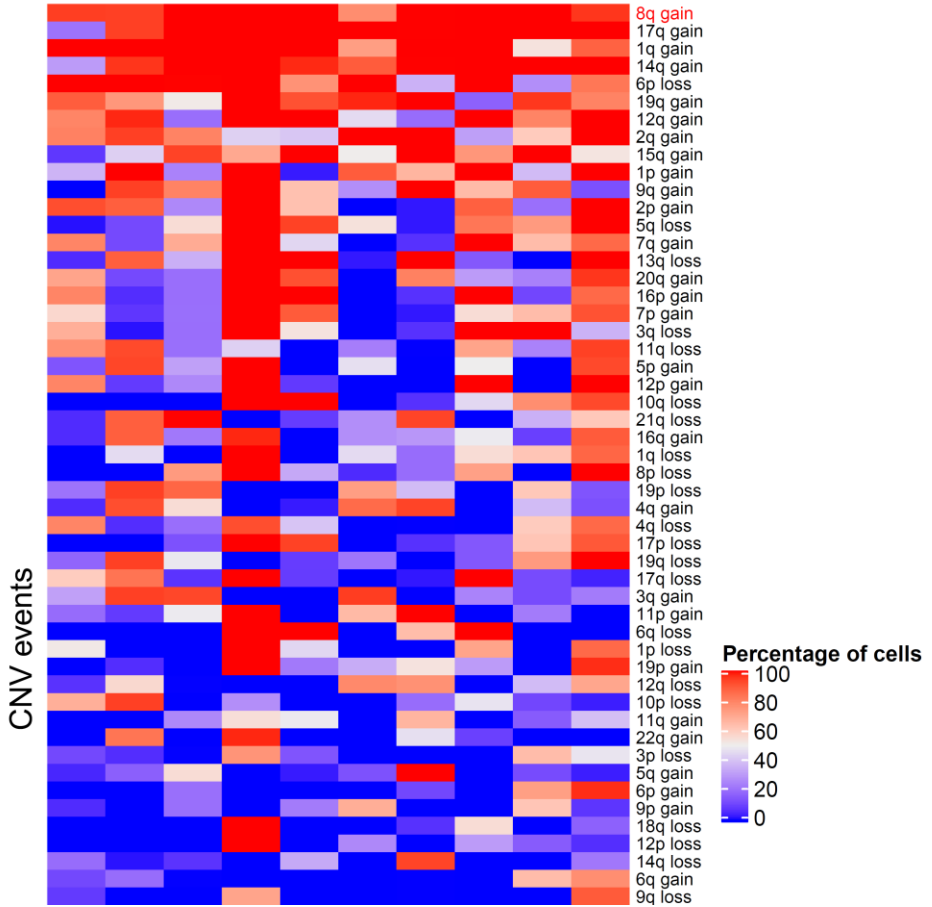
Diagnostic Modality	Sensitivity	Specificity
Anatomic MRI[1]	90%	61%
Image-guided biopsy[2]	73%	100%
cfDNA ULP-WGS (current study), pre-treatment	**75%**	**91%**
cfDNA ULP-WGS (current study), serial analysis	**83%**	**91%**

[1]Wasa et al., 2010
[2]Graham et al., 2019



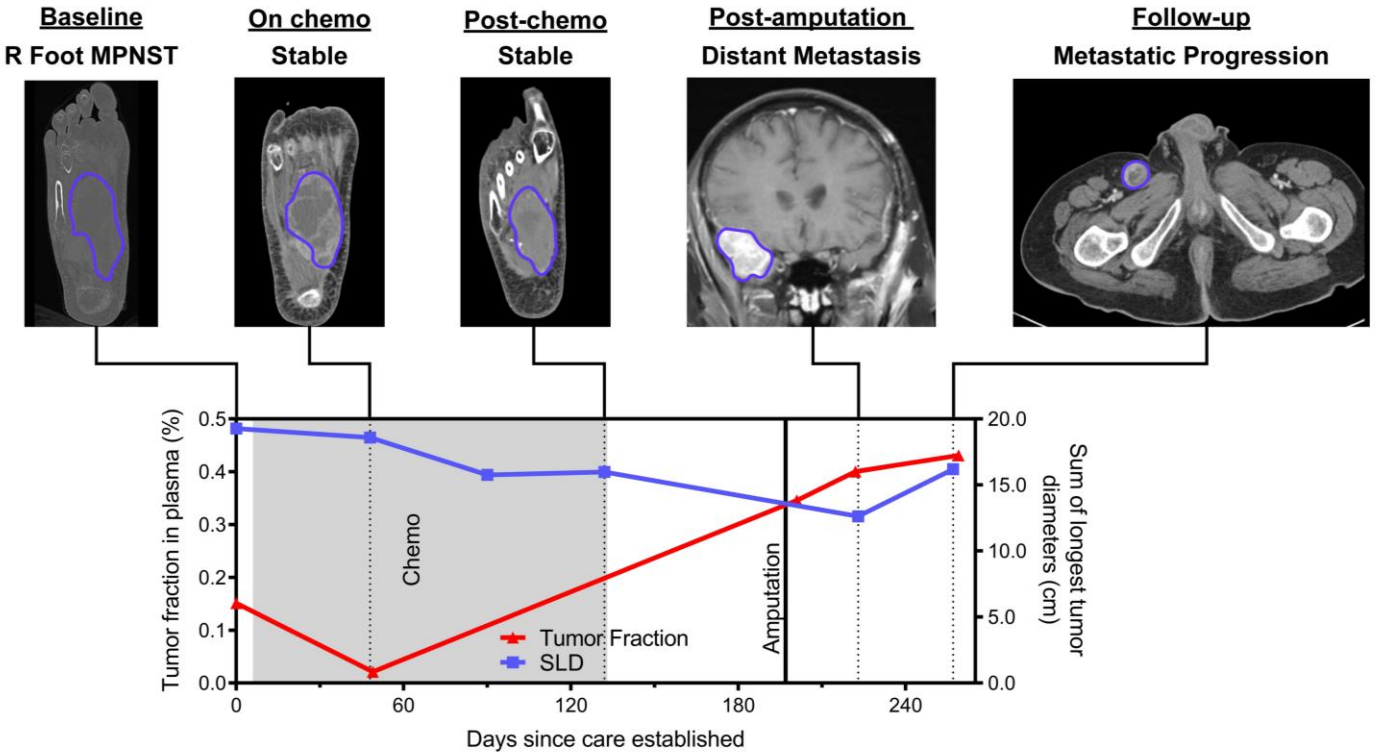
Chromosome 8 gain is an early genomic event in transformation to MPNST





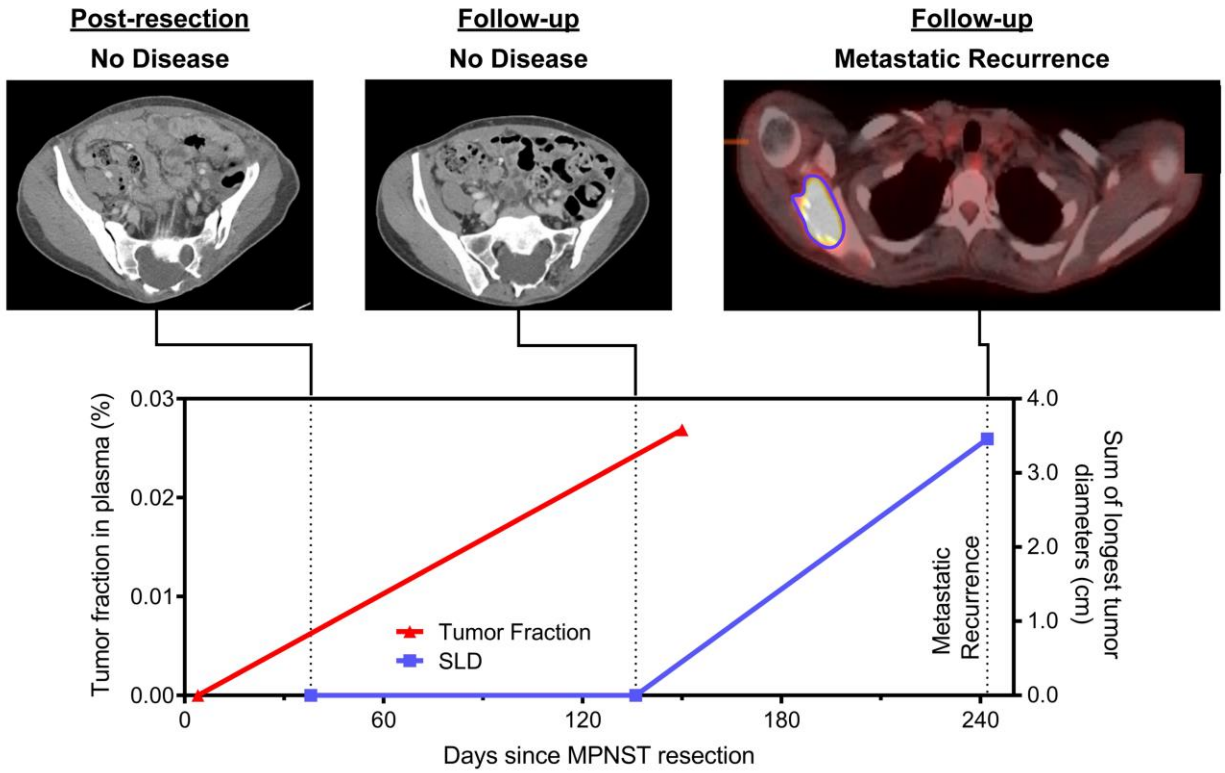
Dehner et al., 2021

Increases in cfDNA Tumor Fraction Precede Radiographic Metastatic Progression



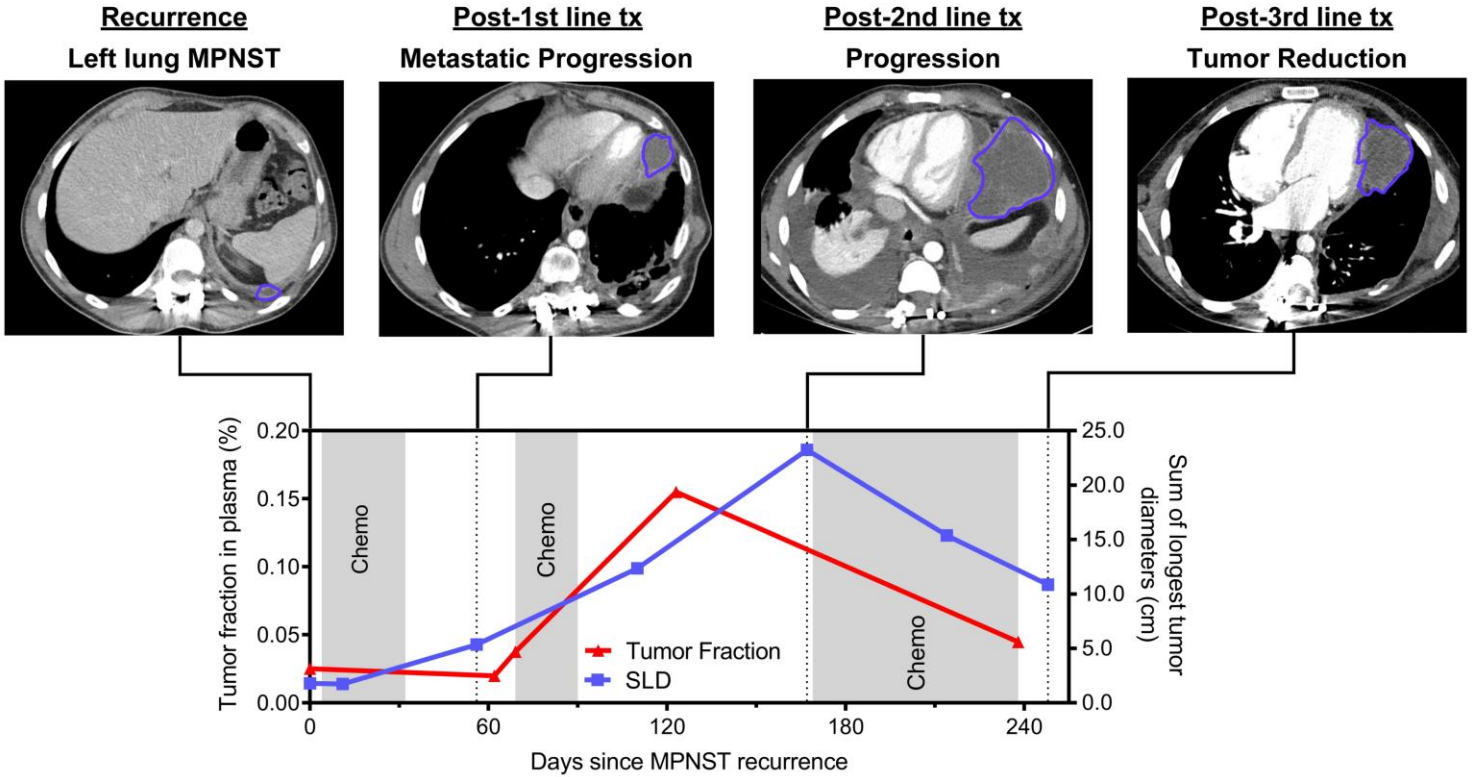
Szmanski et al., PlosMed 2021

Increases in cfDNA Tumor Fraction Precede Radiographic Metastatic Progression



Szmanski et al., PlosMed 2021

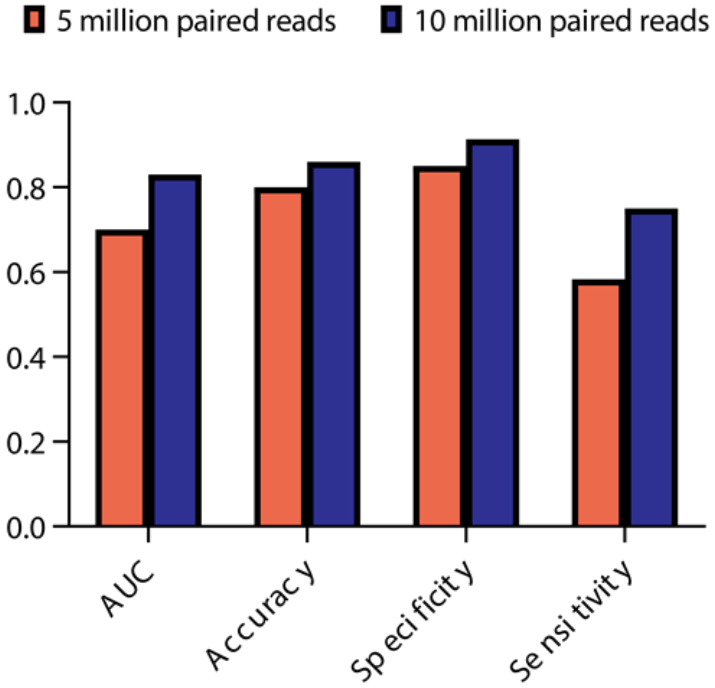
Dynamic Changes in Tumor fraction correlate with response



Szmanski et al., PlosMed 2021

Cell free DNA could be a powerful tool in the pediatric oncology clinic

1. Early cancer detection
   - Particularly useful in the cancer predisposition syndromes
2. Minimal Residual Disease
3. Response to therapy
   - Deeper understanding of tumor clonal evolution in response to therapy



	AUC	Accuracy	Specificity	Sensitivity
5 million paired reads	0.700	0.800	0.854	0.583
10 million paired reads	0.830	0.860	0.913	0.750

Collaborators

NCI, CCR, Pediatric Oncology Branch
Taylor Sundby
Carly Sayers
Xiyuan Zhang
Bega Murray
Haiyen Lei
Brigitte C. Widemann
Andrea Gross
NF1 Clinical Team

Washington University
Angie Hirbe
Divya Srihari
Aadel Chaudhuri
Paul Jones
Jeff Syzmanski
Noah Earland
Peter K. Harris
Matthew B Spraker
Li Ding

NCI, CCR, Genetics Branch
Javed Khan

Childrens Oncology Group
Corinne Linardic
Erin Rudinski
Mike Arnold
Steve Skapek
Dave Hall
Don Barkauskus
Doug Hawkins

Institute of Cancer Research UK
Janet Shipley
Anna Kelsey
Rebecca Brown
Julia Chisholm
Joanna Selfie

NCI DCEG
Kristie Jones
Belynda Hicks

Peyton Arens

St. Baldrick's FOUNDATION
Conquer Childhood Cancers

NATIONAL CANCER INSTITUTE
Center for Cancer Research

ccr.cancer.gov